Analysis of Neonatal Pulmonary Mechanics

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Abstract: Mechanical ventilation (MV) is widely used in the Neonatal Intensive Care Unit (NICU) for patients suffering from respiratory distress syndrome (RDS). MV treatment is difficult due to intra-patient and inter-patient differences in lung mechanics over time, highlighting the need for patient-specific methods. Model-based methods allow identification of patient-specific lung mechanics which can be used to guide care. The aim of this study is to determine if the single compartment lung model can be used with neonatal MV data to provide more insight into their lung mechanics. Neonatal patient data was collected from published literature, and results were compared to data obtained from previously conducted clinical trials in the adult ICU. The single compartment lung model was found to fit the data very well (model fit error range: 2.2 - 6.6%) giving patient-specific elastance and resistance values for each breath. Lung elastance was compared for adults and infants and it was found that infants have ~30x stiffer lungs than adults (elastance: $\mathbf{1-1.75\ cmH_2O/mL}$ vs. $\mathbf{0.017-0.059\ cmH_2O/mL}$) for similar driving pressures. The ventilated neonatal lung has different lung mechanics to an adult's, suggesting that the lung of a neonate should not be treated as a small adult lung. Further work will validate these results using patient data collected from the NICU. Ultimately, this research will provide more knowledge into neonatal pulmonary mechanics and can be used as the first step towards optimised patient-specific care in the NICU.

***Keywords**:* model-based ventilation, identification and validation, physiological model, intensive and chronic care or treatment, decision support and control

1. INTRODUCTION

Mechanical ventilation (MV) is used to support or fully control the breathing of respiratory failure patients, while the cause of failure is mediated or allowed to recover (Hamed et al., 2006). MV is widely used in the Neonatal Intensive Care Unit (NICU) for patients suffering from respiratory distress syndrome (RDS). RDS occurs in neonates, most commonly due to a lack of surfactant (Liggins and Howie, 1972) in the pulmonary system as a result of prematurity of birth.

Surfactant coats the surface of the alveoli, lowering the surface tension of the lung lining, preventing alveolar collapse at end-expiration and reducing the pressure required to achieve inflation (Harding and Hooper, 1996), all of which are beneficial to reduce the work of breathing. The pulmonary surfactant system develops later in the gestation period, with surfactant being produced from ~24 weeks, increasing to full term (Joshi and Kotecha, 2007). As a result, some very/extremely premature neonates (24-32 weeks) have sufficient surfactant production from birth and so, do not develop RDS (Harding and Hooper, 1996). However, a large number of this cohort are not born with sufficient natural surfactant and thus require MV (Harding and Hooper, 1996).

Currently, MV parameters are chosen at the discretion of the specialist based on clinical experience. Specialists could be better guided by having more information available to enable more optimal MV settings for every patient at any given time. Poorly delivered MV treatment can result in unintended additional lung damage, for example over-inflation causing ventilator-induced lung injury (VILI) (Slutsky and Ranieri, 2013), or alveoli can collapse, causing derecruitment and VILI. To prevent derecruitment, a minimum baseline pressure is required to hold the alveoli open at the end of expiration, called Positive End Expiratory Pressure (PEEP) (Gattinoni et al., 2010). If PEEP is too high or low damage may be caused (Slutsky and Ranieri, 2013).

In addition to selecting the correct parameters, specialists must also choose between different ventilation modes. Selection may depend on the patient and the reason for initiating MV, as well as varying between ventilator modes. There are no universal standards or protocols for delivering MV in response to care and as condition evolves (Dickson, 2014, Sundaresan et al., 2011). All these issues highlight the need for a patient-specific treatment method or protocol to provide optimised care for each patient (Sundaresan et al., 2011). In addition, there are differences in MV terminology between ventilator modes and units (Donn, 2009, Chatburn, 2007).

Model-based methods can be used to identify patient-specific lung mechanics that would otherwise be unmeasured directly (Chiew, 2013, Chiew et al., 2011). As a result, model-based methods have been developed for the adult ICU to guide and optimise medical care provided (Sundaresan et al., 2011, Szlavecz et al., 2014). The single compartment lung model is just one example of many (Ben-Tal, 2006). It has been extensively studied and can be used to determine the breath-to-breath elastance of the lung and airway resistance in adult

ICU MV patients (Chiew, 2013, Bates, 2009, Chiew et al., 2015a, Chiew et al., 2015b, Sundaresan et al., 2011).

This study aims to determine if the single compartment lung model can be used to study neonatal pulmonary mechanics using clinical data sourced from published literature. While this model has been used in adults, the model has never been applied to the infant lung. The key outcome is to apply a model-based approach to analyse NICU MV patients and compare the mechanical lung properties to those of adults. The analysis will assess if a neonatal lung can be treated as simply a "small adult lung" since adult RDS patients are commonly referred to as having a "baby lung" (Gattinoni and Pesenti, 2005). If the model can fit the data well and capture the measured mechanics and dynamics, this study could be a first step towards patient-specific MV in the NICU.

2. METHODS

2.1 Neonatal Patient Data

A literature search was carried out using Google Scholar and PubMed with key search terms: Neonatal, Infant/baby Mechanical Ventilation, NICU. Studies were included if they presented airway pressure and flow data from infant and premature neonates in a graphical format with the full waveforms clearly displayed and distinguishable. Waveform data was extracted using image processing software (Tummers, 2006). Individual breaths were identified on the basis of flow with zero flow signifying the start and end of inspiration and expiration. Included studies are summarised in Table 1. All web-based studies were accessed between May and July 2016. The data provides a broad range of cases, MV modes, and PEEP, enabling a full analysis of the model's ability to be used with this data, which is the primary goal of this analysis. PEEP was noted to seem to be relatively consistent across the studies.

2.2 Adult Data Comparators

For comparison to neonatal data, the single compartment lung model was also fit to adult clinical data from patients over the age of 16 at the Christchurch Hospital, New Zealand (Chiew, 2013). This data included 10 invasively ventilated (Puritan Bennet PB840), sedated and muscle relaxed patients. Volume controlled ($V_t = 4{\sim}6\, ml/kg$) SIMV mode was used throughout the trial and PEEP was clinically titrated to patient condition at the bedside. This trial was approved by New Zealand, South Island Regional Ethics Committee (UTA: U1111-1125-7363; ACTRN: 1261-1001-1799-21).

Recruitment manoeuvres (RM's) were performed during the trial. At the start of the RM, the clinically selected PEEP was decreased to zero PEEP (ZEEP) for 5 breathing cycles. PEEP was then increased in increments of 5 cmH_20 from ZEEP until peak airway pressure (PIP) reaches a limit of 45 cmH_20 (Gattinoni et al., 2006). Every subsequent PEEP level was maintained for 10 breathing cycles before increasing to a higher PEEP. After reaching 45 cmH_20, PEEP was reduced by steps of 5 cmH_20 to a clinically selected PEEP. Throughout the trial, other ventilator settings were not changed.

2.3 Single Compartment Lung Model

The single compartment lung model is a lumped parameter model that characterises fundamental lung mechanics to identify patient-specific lung elastance (E_{rs}) and resistance (R) (Chiew, 2013). The model identifies these variables from airway pressure (P_{aw}), volume (V, found by integrating flow for each breath), flow (Q), and PEEP (P_O), and is defined:

$$P_{aw} = E_{rs}V + RQ + P_O \qquad (1)$$

The model was fit over inspiration, where the onset of a breath was defined as the point where flow becomes positive. The end of inspiration was defined as the point where flow becomes negative. The first 10% of each breath was removed as they can contain unwanted artefacts as a result of ventilator operation, providing the best model fit across all patients. E_{rs} and R were identified via the integral method (Hann et al., 2005, Chiew et al., 2015b).

Table 1: List of published sources used in data collection.

Sources	Patients	# Breaths recorded
(Muramatsu et al., 1992)	1	1
(Brown and DiBlasi, 2011)	1	1
(Bancalari and Claure, 2015)	1	9
(Klingenberg et al., 2011)	5	20
(Donn, 2009)	2	17
(Mammel, 2006)	9	35
(De Jesus and Petty, 2012)	2	13

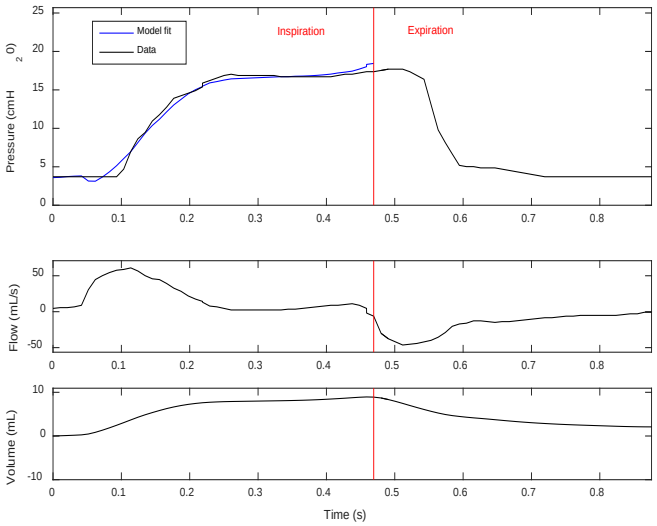

Figure 1: Pressure with inspiration model fit for pressure controlled MV (Top), flow rate (Middle), and volume over time for single breath (Bottom). (Brown and DiBlasi, 2011).

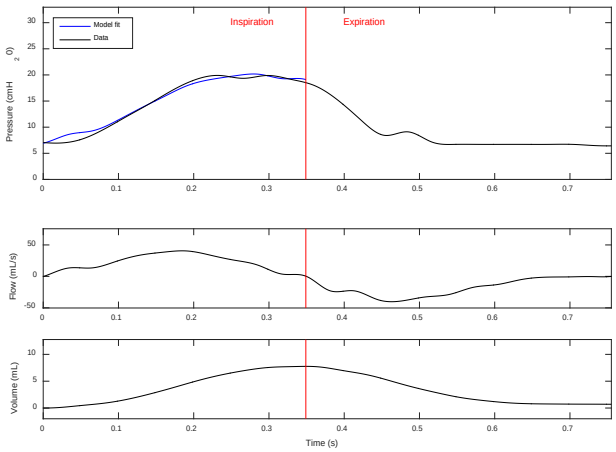

Figure 2: Pressure with inspiration model fit (Top), flow rate (Middle), and volume data over time for single breath (Bottom). (Klingenberg et al., 2011)

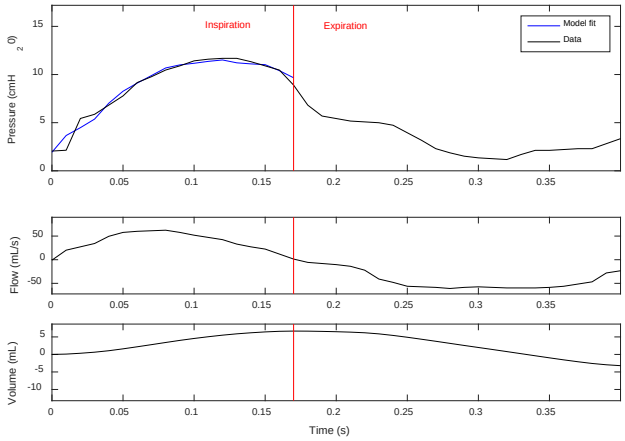

Figure 3: Pressure with inspiration model fit for SIMV (Top), flow rate (Middle), and volume over time for single breath (Bottom). (Mammel, 2006)

3. RESULTS

3.1 Neonatal Lung Mechanics

Figures 1-3 show the fit for three example breaths over inspiration. The pressure and flow data was obtained from (Mammel, 2006, Klingenberg et al., 2011, Brown and DiBlasi, 2011) and cover pressure controlled, volume guaranteed breathing and SIMV modes, respectively. In each case, the fit of the model to pressure is very good, indicating the model captures all fundamental observed dynamics. With a model fit error of 3.45%, 3.94% and 7.75%, respectively, the model seems to fit a range of different MV modes.

Over all 21 NICU data sets, there was a large spread of values for the identified lung elastance, as shown in Table 2. Tidal volumes are much lower than in adults, ranging from $5-30\ mL$ with an outlier at approximately $70\ mL$. In general, the elastance values for infant lungs were found to be in the approximate range of $1-1.75\ cmH_2O/mL$, with smaller elastance values in patients with larger tidal volumes. The

Table 2: Literature data summary and model fit parameters. V_t is tidal volume, Q_{in} is maximum flow rate, ΔP is the pressure range, E_{in} the elastance, and R the resistance

Reference	Model fit error (%)	V_t (mL)	V_t/kg	Q_{in} (mL/s)	PEEP (cmH_2O)	ΔP (cmH_2O)	E_{in} (cmH_2O/mL)	R (cmH_2O/mL/s)	Δ P/kg	Weight (kg)	MV Type
(Muramatsu et al., 1992)	6.57	66.6	25.9	35	3	22.67	0.35	0.009	7.5-8.7	2.57-3.04	P A/C
(Brown and DiBlasi, 2011)	3.46	9	-	15	3	13.40	1.56	0.074	-	-	P A/C-IM
(Bancalari and Claure, 2015)	4.96	6.87	-	14.9	4.3	11.88	1.74	0.0767	-	-	SIMV
(Klingenberg et al., 2011)	3.94	4.98	6.6	18.9	4.8	13.08	1.52	0.090	10.9	0.75	A/C+VG
	8.16	4.87	5.7	16.8	5.9	9.28	1.47	0.204	10.9	0.85	A/C+VG
	1.55	4.4	-	17.5	5	20.39	2.62	0.322	-	-	A/C+VG
	5.79	4.22	-	17	4.9	12.02	2.90	0.010	-	-	PSV+VG
	2.32	3.4	-	10.1	5	11.17	3.18	0.068	-	-	PSV+VG
(Donn, 2009)	6.23	19.4	-	39.8	4	16.17	0.49	0.151	-	-	SIMV
	2.18	19.2	-	47.3	3.6	15.43	0.65	0.073	-	-	A/C
(Mammel, 2006)	7.75	6.7	-	20	2	10.19	1.13	0.077	-	-	SIMV
	3.21	4.4	4.4	24.0	6	13.7	3.01	0.037	13.7	1.0	P A/C
	6.07	11.1	5.4	21.7	5	15.2	1.28	0.132	7.4	2.06	TCPL A/C
	4.49	11.8	6.1	23.6	5	15.8	1.22	0.119	8.1	1.94	P A/C
	6.30	11.4	6.1	25.2	5	15.5	1.29	0.157	8.3	1.87	P A/C
	7.36	9.92	5.3	38.4	5	15.0	0.98	0.099	8.0	1.87	TCPL A/C
	5.18	12.2	6.2	34.9	5	16.7	1.32	0.050	8.5	1.97	P A/C
	3.95	27.1	14.0	73.2	5	16.6	0.49	0.056	8.6	1.94	P A/C
	6.51	11.2	5.4	34.7	5	14.9	1.37	0.052	7.2	2.07	HFOV
(De Jesus and Petty, 2012)	2.25	30.1	-	50.3	4.6	15.00	0.44	0.051	-	-	SIMV
	3.02	10.4	-	46.7	6.8	9.19	0.59	0.055	-	-	HFOV

Note: Modes; P = Pressure, A = Asynchronous, C = Controlled, IM = Intermittent, SIMV = Synchronized IM Ventilation, TCPL = Time Cycled Pressure Limited, VG = Volume Guarantee

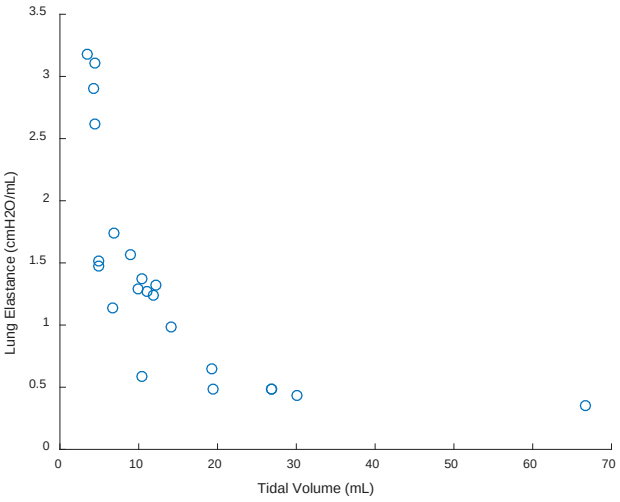

Figure 4: Distribution of infant lung elastance values over tidal volume

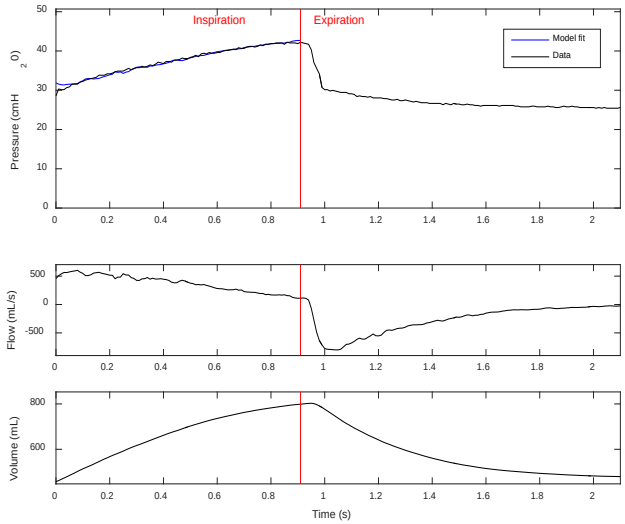

Figure 5: Pressure (top) and model fit, flow (middle) and volume (bottom) data from Adult ICU patient

relation between elastance and tidal volume (V_t) appears to be strongly exponential or hyperbolic (Figure 4). There was a grouping of elastance values greater than 2.5 cmH_2O/mL that were outliers at very low tidal volumes. Table 2 shows the full results, including all parameters and identified variables. The resistance values were found to agree with that of Sly et al. The resistance is known to vary with the diameter of the endotracheal tube (ETT) and flow rate used during MV (Sly et al., 1988).

3.2 Comparison of Neonatal and Adult Lung Mechanics

The model fit over inspiration for an adult patient with chronic obstructive pulmonary disease (COPD) ventilated with pressure controlled SIMV (Chiew, 2013) is shown in Figure 5, with a range of $0.017 - 0.059\ cmH_2O/mL$. The relatively large tidal volume of approximately 800 mL is much larger (10-100 times) than in neonates. However, at PEEP $= 25\ cmH_2O$, a driving pressure of $\Delta P \cong 17\ cmH_2O$ is similar or only slightly larger than the neonates in Table 2. Thus, it is clear that overall elastance is significantly lower for adults.

Elastance values for all neonatal and adult patients were plotted to identify any correlations and is shown in Figure 6. A curve is fit through the adult data that is linear for a logarithmic y-axis elastance scale. If neonates lay along this same linear line as "small adults" (curve in log_{10} scale), then their data would be around that line. However, it is clear that neonates have much higher elastance ($p \sim 0.0$) since the lowest neonate elastance is greater than the highest adult (Motulsky, 2014).

4. DISCUSSION

4.1 Single Compartment Lung Model Feasibility

The aim of this study was to determine if a single compartment lung model can be used to study mechanics in the NICU. The results clearly show that the model does fit the infant data with minimal error where average error was 4.82% (Table 2). Hence, the model could be used without modification to estimate breath-to-breath lung elastance and resistance based on this first analysis.

The trend line shown for the adult data in Figure 6 is where the neonatal data would be expected to fall if neonates are simply "small adults". However, the assumption of neonates being "small" adults, or vice versa, does not hold. The results clearly show that for similar driving pressures, neonates have approximately 30 times stiffer lungs than adults due to their much smaller overall tidal volumes and overall prematurity. This result follows the trend of the findings by Pandit et al (Pandit et al., 2000), and thus clearly shows that the ventilated neonatal lung has different lung mechanics. Thus, they cannot be considered as a small adult lung, which may have implications for clinical practice around mechanical ventilation and care.

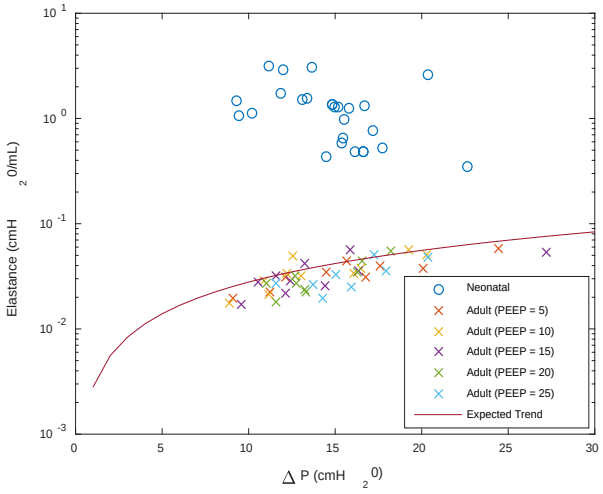

Figure 6: Neonatal and adult lung elastance values at similar driving pressures

Anomalies are present in the results shown in Figure 4 where some patients show even higher than expected lung elastance. Patients who had elastance values above $2.5 - 3\ cmH_20/mL$ were also noted to have relatively very small tidal volumes of $3.4\ mL$ and $4.4\ mL$. These babies are likely to be extremely premature. The more premature the infant, the less developed the lung is, with well-known deficiencies in surfactant production (Liggins and Howie, 1972) and fewer and underdeveloped alveoli (Hislop et al., 1986). These features, alongside the mechanics of inflating smaller volumes, may contribute to higher elastance in more premature babies.

The change in pressures (ΔP) were typically similar for both adults and neonates. However, the tidal volumes (ΔV) for neonatal treatment have been identified to typically be 10 - 50 times smaller. Figure 4 suggests that elastance is a function of tidal volume. This is not unexpected, as a smaller volumetric compartment with similar wall stiffness will look overall more incompliant (higher elastance), requiring higher driving pressures to inflate. Future work will assess the relative contribution of smaller tidal volumes to the higher elastance observed, and the contribution of tissue stiffness and alveolar immaturity. However, although preliminary work suggests that this higher elastance is not solely due to low inflation volume.

Model-based methods have the potential to significantly improve MV treatment for adults in the ICU (Sundaresan and Chase, 2012). These results provide a step toward implementing patient specific MV protocols in the NICU that specialists can use as a guide towards providing more optimised care.

4.2 Limitations

The data was sourced from literature which has been published and reviewed. However, there is potential for there to be errors with the methods used to digitise the data. The image processing software is not perfectly accurate and thus, the results are somewhat limited in accuracy. While this error still has the potential to be significant, the results are similar between different studies, and behave as might be expected. This outcome provides some added validation to the methods used to obtain data, and to the results.

The study used any data available in literature from both sedated and unsedated neonatal patients. A potential limitation in this study is the interaction between spontaneous breathing and underlying respiratory mechanics, which could alter the resulting elastance. However, in this data, there was no pressure drop below PEEP at the beginning of inspiration, which we have observed elsewhere in neonates spontaneously breathing. Thus, the results of this study are likely indicative of expected respiratory mechanics parameters. Further work is required, and underway, to examine the effect of spontaneous breathing on the PV curve, and the degree of influence in the NICU.

In addition, collection of further ventilation data from the NICU and the analysis with the same methods is required to verify the results. An observational trial is currently underway, collecting 24 hours of ventilation data from premature and term infants undergoing conventional and high frequency mechanical ventilation in a NICU. This data would provide more accurate recordings of the patient's flow, pressure and volume. The results presented here provide the justification for such an observational trial.

5. CONCLUSIONS

A single compartment lung model was fit to data to describe lung elastance and resistance in premature neonates and infants. The average fit error was 4.82%, suggesting that the model is able to capture infant lung mechanics and dynamics. Comparison of adult and neonatal lung mechanics showed that neonatal lungs have much higher elastance than adults for similar driving pressures. These differences in mechanical properties have implications for MV treatment, as the lung of a neonate should not simply be considered as a "small adult" lung. This study creates the possibility of using model-based methods to develop patient-specific MV treatment protocols in the NICU, leading to more optimised and effective care.

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